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| 08/653,294 | 05/24/96 | CLAYBERGER C | 286002020023 |

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| **ART UNIT** | **PAPER NUMBER** |
| 1816 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**



☆U.S.GOVERNMENT PRINTING OFFICE 1995-319-826

| Office Action Summary | Application No. 08/653,294 | Applicant(s) Clayberger et al. |
|---|---|---|
| | Examiner Thomas Cunningham | Group Art Unit 1816 |

☒ Responsive to communication(s) filed on *Mar 20, 1997*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-26* is/are pending in the application.

Of the above, claim(s) *22-26* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-21* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

1. Claims 1-21 are active.

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-21, drawn to peptide products, compositions and methods, classified in class 530, subclass 300, 350 or 403 and Class 424, subclass 185.1.

II. Claims 22-25, drawn to nucleic acids, classified in class 536, subclass 23.1.

III. Claim 26, drawn to antibodies, classified in class 530, subclass 387.1.

1. The inventions are distinct, each from the other because of the following reasons: Inventions I, II and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are directed to peptides, nucleic acids and antibodies, products which have materially different structures and functions..

2. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

3. During a telephone conversation with Robert Millman on 5/19/97 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-21. Affirmation of this election must be made by applicant in responding to this Office action. Claims 22-26 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(h).

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 C.F.R. § 1.67(a) identifying this application by its Serial Number and filing date is required. See M.P.E.P. §§ 602.01 and 602.02. The oath or

declaration is defective because:

A. Assuming priority to applications prior to the filing date of 08/222,851 is being claimed, the oath/declaration does not refer to the U.S. priority applications prior to 08/222,851. (The first page of the specification does not recite applications filed prior to 08/222,851 for purposes of 35 U.S.C. 120 either.)

B. It does not state that the person making the oath or declaration in a continuation-in-part application filed under the conditions specified in 35 U.S.C. § 120 which discloses and claims subject matter in addition to that disclosed in the prior copending application, acknowledges the duty to disclose material information as defined in 37 C.F.R. § 1.56(a) which occurred between the filing date of any application prior 08/222,851 and the national or PCT international filing date of the continuation-in-part application.
If Applicant intends to limit the priority claim to the filing date of 08/222,851 (04/05/94), this should be so stated, and this objection will be dropped.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as the invention.

7. Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph as failing to particularly point out and distinctly claim the invention.

A. Claim 18 is vague and indefinite as to the metes and bounds of "MHC unmatched donor". Does this term limit the donor to one who has no MHC Class I or MHC Class II alleles in common with the recipient? Are different subtypes of the same allele (e.g. HLA-B27.01 and HLA-B27.02) considered matches?

B. In claim 18 is not clear what the characteristics of a "predetermined regimen" are. Does this term limit the claimed method to any particular series of steps? Does this term require that the predetermined regimen be a series of steps approved by the FDA?

C. In claims 18-20 the term "extend the period of acceptance" or "inhibit transplant rejection" are vague and indefinite because it is unclear how this is to be measured in an objective manner, what is the control? If only a single patient is treated, how would one know whether the period of acceptance has been extended?

D. In claim 19 the phrase "subtherapeutic dosage" is vague and indefinite. Does this refer to a dosage of a conventional, known immunosuppressant that is incapable of extending the period of acceptance by itself?

E. In claims like 19-20 it is unclear what the metes and bounds of the term "immunosuppressant" are. Is this limited to particular, conventional immunosuppressants such as cyclosporin? Does it embrace anti-T cell antibodies, e.g. anti-CD4 or anti-TCR antibodies? Does it embrace superantigens? Does it embrace biological agents such as immunodeficiency viruses? Applicant is invited to point out the portion of the specification which defines this term.

F. In claims like 1 and 21 it is unclear what the metes and bounds of the term "peptide-type" compound are. Is this limited to peptides having either L- or D-amino acids? Is this term limited to peptides with consisting of all L-isomers of amino acids, but having chemically modified N or C termini? Does this encompass other types of non-peptide mimetics? Does this term encompass peptide conjugates, multimerized peptides, or dendritic polymers (e.g. MAPS)? Applicant is invited to point out the definition of this term in the specification and clearly explain its limits. In claim 1, what is the difference between a "peptide-like compound" and a "variant" thereof? In claim 1, last two lines, it is also unclear how a "peptide-type bond" differs from a "peptide bond".

G. In claim 1 it is unclear which amino acids are "hydrophobic or small" amino acids.

H. In claim 1 what are the metes and bounds of the term "immunomodulating". Broadly interpreted this term would encompass any affect on any component of the immune system. Is this term intended to be limited to compounds which modulate particular types of CTL activity, e.g. proliferation or cytotoxicity?

I. It is unclear whether the language of claim 1 is open or closed. Is the recited compound limited to peptides 60 amino acids or less?

J. In claim 1 the word "brackets" has been interpreted to referring to this type of bracket "{ }" and not to the parenthesis "( )".

8. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for particular peptides such as the sequences demonstrated to inhibit cytolysis on pages 21-et seq. of the specification, does not reasonably provide enablement for all the peptides encompassed by broad claim language.

A. In vivo usage not enabled. One with skill in the art would not reasonably expect to be able to use the claimed compounds, peptide compounds and peptide conjugates because it would be unpredictable and require undue experimentation to determine whether such peptide-based products would exert functionally useful effects on CTL responses in vivo. Peptide compounds that comprise allogeneic (non-self) alpha-1 domain sequences would be

expected to be recognized as foreign by a subject and eliminated. Further, short peptides, in general, when administered in vivo would be expected to be degraded or metabolized by host mechanisms, such as by serum proteases, or hepatic or immunological clearance mechanisms prior to exerting useful effects of a subject's CTL's. Additionally, one would expect that effective concentrations of the claimed peptide products could not be achieved in vivo, due to the aforementioned clearance mechanisms, or the presence of anatomical barriers limiting their access to a subject's CTL's.

B. Xenotransplantation. The specification does not provide a reasonable expectation that the claimed methods could be used to extend the period of acceptance for xenogeneic transplants. There is no claim language limiting the claimed methods to transplants within a particular species, e.g. allogeneic transplants. Due to the genetic differences between MHC, T cell receptor, and accessory molecule determinants of different species, one with skill in the art would not expect that MHC protein sequences from one species (e.g. the HLA molecules of humans) would be capable of blocking immune responses in another species. Although there is description of xenogeneic organ transplants on page 22, line 18 of the specification, one with

skill in the art would not have a reasonable expectation that the claimed peptides would prolong the survival of such xenogeneic transplants for the reasons set forth above.

C. Allotransplantation/MHC Restriction. The methods have not been limited to inhibition of CTL's which have shared MHC specificity with the administered peptide. According to page 26 of the specification of the parent application 08/222,851 "The results in Table 2 indicate that only whether the CTL's and the target cells share A2 specificity do the A2-derived peptides provide inhibition". E.g. the administered peptide would have to be matched to the HLA type of the transplanted organ, and would be expected only to inhibit that portion of host CTL response directed to that particular HLA molecule.

Thus, where a transplanted organ has multiple HLA, other antigen mismatches with a host, administration of a single peptide would be expected to at best reduce immune response to a single HLA antigen. Whether, reduction of only a portion of the CTL response would result in a prolongation of graft survival by reducing rejection phenomena below a particular threshold would be unpredictable.

D. Regimen. The ability of the claimed methods to prevent rejection depends on the particular steps in the regimen, see e.g. page 14 of the specification. The claims have not been limited to regimes that would be expected to reduce rejection of allo- or xenografts. E.g. oral or inhalational administration of the peptides would not be expected to put them in contact with CTLs mediating graft rejection. Whether the peptide is administered prior to allografting or after would also be expected to be critical to the type of suppressive effect achieved, see e.g. page 31, lines 17-19 of the specification which indicate that timing of the dosages is critical.

E. Diverse peptides. Claims 1-12 reads broadly on use of peptides comprising residues 75-84 of any HLA-B alpha chain. However, page 40, lines 1-5 indicate that only peptides having sequences corresponding to particular alleles of HLA-B alpha 1 block CTL responses. E.g. HLA-B2702 blocks, but HLAB2705 does not. It would be unpredictable which peptide species would be capable of multiallele blocking without testing of different peptide species on a case-by-case basis. For instance, pages 21-22 of the specification disclose that the HLA-B2702.75-84 and HLA-B2705.75-84 peptides, though differing in only three residues have materially different effects: the HLA-B2702 peptide

inhibited lysis; the HLA-B2705 peptide did not.

F. Variants. Claims 1-21 also encompass variants of the recited (HLA-B derived) peptide sequences. It would be unpredictable which mutations of an HLA-B 75-84 sequence would retain the critical functional property of being able to inhibit CTL activity because such mutations would be expected to affect functional binding of the peptide to the T cell receptor or accessory molecules. Modifications to the recited peptides, whether the addition, substitution, or deletion of amino acid residues, or the joining of such peptides to other chemical moieties would be expected to have unexpected, unpredictable effects on the activity of the particular peptide to modulate CTL responses, see e.g. Bowie, et al., Science 247:1306-1310 (1990). It is unclear how the peptides are actually modulating CTL responses, but one with skill in the art would expect that the claimed peptide compounds are interfering with the T cell receptor (TCR) antigen presenting cell interaction. It is unclear on a structural basis which types of modifications can be made to a "blocking" or stimulatory peptide and still have it exert its functional effect. For instance a stimulatory peptide that had bulky, sterically hindering chemical moieties joined to it would not be expected to effectively stimulate CTL responses,

because the additional moieties would be expected to prevent it from binding to the sites on the CTL or the APC necessary for inducing CTL stimulation. Each chemical modification of a peptide known to modulate CTL activity would have to be investigated on a case-by-case basis and thus would impose a burden of undue experimentation on one with skill in the art.

G. Subtherapeutic dosage. The specification does not adequately describe the parameters of the term "subtherapeutic dosage", as used e.g. in claims 19 and 20. Does an immunosuppressant in a subtherapeutic dosage have no effect on transplant survival time? How would one with skill in the art determine what was or was not a subtherapeutic dosage of a particular immunosuppressant?

H. Immunosuppressive agent required. According to page 31 of the specification allograft survival was similar in control and peptide-treated groups> Only groups treated with CsA had significant increases in graft survival time.

I. The recited immunomodulating activity, see e.g. claim 1, appears to be limited to reductions in CTL cytotoxicity or proliferation. The specification does not describe that other types of immunological mechanisms are affected by treatment with

the recited peptides. See e.g. the lack of activity of the recited peptides on antibody responses as mentioned in section G of page 34 of the specification.

J. The compound of claim 1 appears to be a peptide homo- or heterodimer. One would expect that only certain types of dimeric compounds have the ability to reduce CTL responses because different configurations of dimers would have different structures or spacing of determinants, and therefore different functional abilities to compete or bind to T cell ligands or MHC Class I molecules. Since a particular mechanism of action for the peptide dimers has not been adequately described, it would be unpredictable which structures would retain functional activity.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In

considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olsson, U.S. patent 5,073,540 or WO88/05784 (published 11 August 1988). Olsson disclose peptides useful as antagonists or agonists for membrane receptors. The prior art compounds have essentially the same structure as those of the instant application, see e.g. cols. 7 and 8. WO88/05784 discloses similar peptides, see e.g. claim 1.

It would have been prima facie obvious to one of ordinary skill in the art at the time of invention to modify the prior art peptides and to test functional activity on surface receptors or lymphocyte activity of the modified peptides using the assays disclosed in Olsson cols 12-14 or by WO88/05784 page 25.

Further, page 40 of WO88/05784 explicitly suggests use of such peptides for prolonging graft survival time by reducing rejection cytolytic CTL activity.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas M. Cunningham, Ph.D, J.D. whose telephone number is (703) 308-3968. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. ENDFIELD

TMC

THOMAS M. CUNNINGHAM
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GROUP 1800